연구 Design 적절성 평가

김창수

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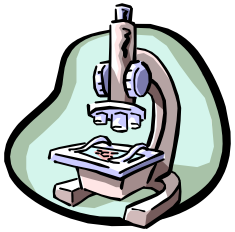
Executive Editor, Yonsei Medical Journal

Medical Research



Basic Science

Clinical Science

Population Science

What is Clinical Research?

"… a component of medical and health research intended to produce knowledge essential for understanding human disease, preventing and treating illness.

Clinical research embraces a continuum of studies involving interaction with patients, clinical materials or data, or population …"

- **a broad definition from AAMC(Association of American Medical Colleges) Task Force on Clinical Research (2000) -**

Categories of Clinical Research

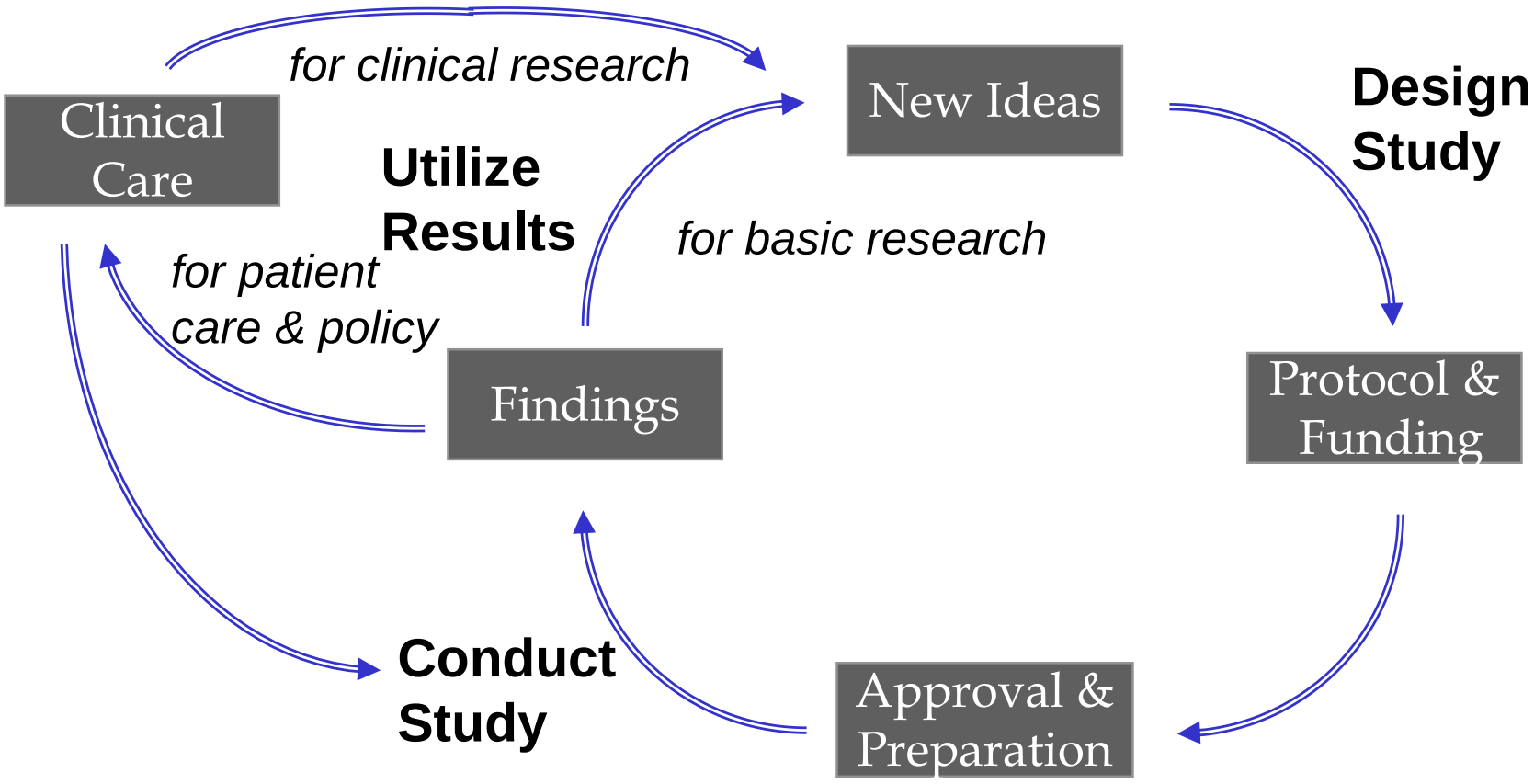
- **Disease mechanism**
- **Translational research**
- **Clinical knowledge**
- **Diagnosis/natural history of disease**
- **Therapeutic interventions including clinical trials**
- **Behavioral research**
- **Health services research**
- **Epidemiology**

For most clinicians, in practice…

Research in clinical setting involving subjects who are patients with a disease of interest..

- **Clinical trials or therapeutic research**
- **Clinical epidemiology: disease diagnosis and prognosis**
- **Clinical audit/ QA study: health outcomes, clinical performance monitoring**
- **Clinical Economics: cost-effectiveness of healthcare**
- **Disease epidemiology: incidence, prevalence, distribution of and risk factors for disease X**

Research and Care together



Classification of Clinical Research

- **Experiment**
  - **Randomized Clinical Trials**
- **Obervation**
  - **Cohort study**
  - **Case-control study**
  - **Cross-sectional study**
  - **Ecological study**
- **Case-series report**
- **Case-report**

CAUSATION?

1. Case definition: adverse event

2. Frequency measurement

3. Measures of morbidity or mortality

1. Case Definition

A case definition is **a set of standard criteria** for deciding whether a person has a particular disease or other health-related condition.

By using a standard case definition we ensure that every case is diagnosed in the same way, regardless of when or where it occurred, or who identified it.

2. Frequency measurement

- 비(Ratio)
- 분율(Proportion)
- 율(Rate)
- 보통율, 특수율 및 표준화율
  (Crude, specific and standardized rate)

2-1. 비(Ratio)

- 한 측정값을 다른 측정값으로 나눈 값
  - 분자가 분모에 포함되지 않는 경우를 의미함
  - A : B 또는 A/B의 형태로 표현됨

예) 성비(sex ratio),
비교위험도(relative risk),
교차비(odds ratio)

2-2. 분율(proportion)

- 전체 중에서 어떤 특성을 가진 소집단의 상대적 비중을 나타냄
- 분자가 분모에 포함됨(주로 %로 표현)
  - A/(A+B)의 형태로 표현됨
  - 0 에서 1사이의 값을 가짐

예)치명률(fatality rate)

누적발생률(cumulative incidence rate)

유병률(prevalence rate)

2-3. 율(rate)

- 율(rate)=일정기간동안 사건의 발생수

$$\text{율(rate)} = \frac{\text{일정 기간동안 사건의 발생수}}{\text{일정 기간 동안 평균 인구수}}$$

- 율은 시간의 개념이 포함되어 있음

Measures of disease occurence

Prevalence

measures population disease status

Incidence

assess frequency of disease onset

- Cumulative incidence or incidence proportion
- Incidence density or incidence rate

Survival rate

Case-fatality rate

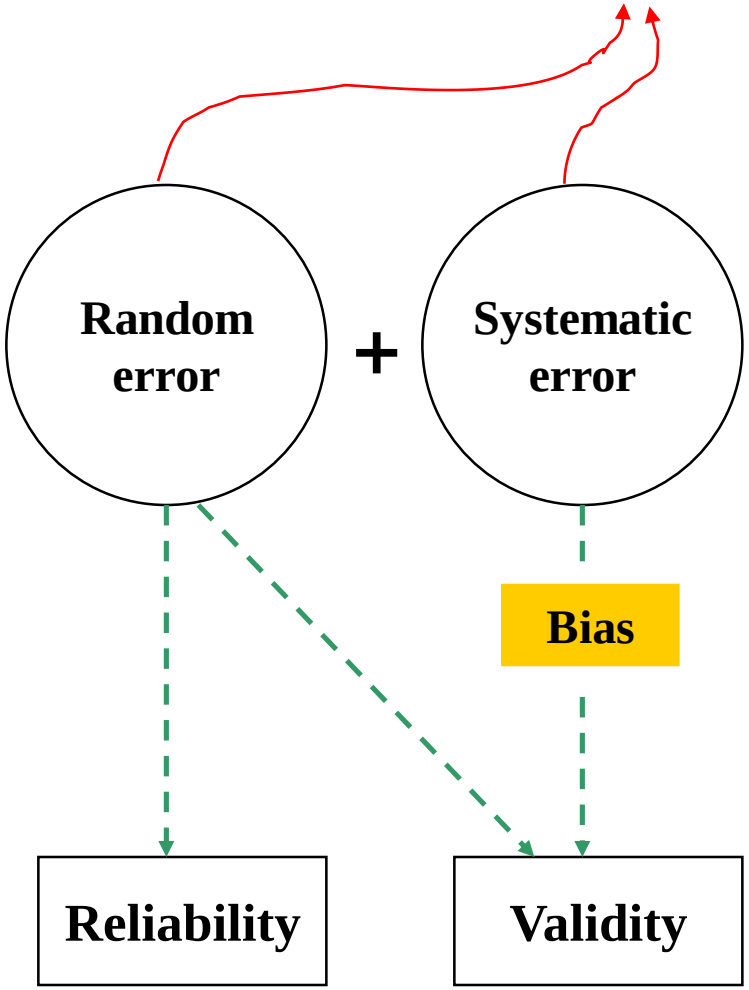
Selecting an appropriate statistical test

- **Type of research question posed by the study**
  - Association between putative risk factor and a disease
  - Differences between comparison groups
    - Comparing therapeutic or diagnostic options
- **Type of data collected**
  - Categorical data (count, frequency)
    - Nominal scale, Ordinal scale, Interval / ratio scale
  - Continuous data or quantitative measurements
    - Converted into Ordinal or Interval / ratio scale
- **Type of study design**
  - Observational design : cohort, case-control, cross-sectional
  - Experimental studies : randomly allocate subjects to comparison groups

Types of association between factors under study

- None: independent
- Artifactual: spurious or false
  - Chance: unsystematic variation
  - Bias: systematic variation
- Indirect: confounding
- Causal: direct or true

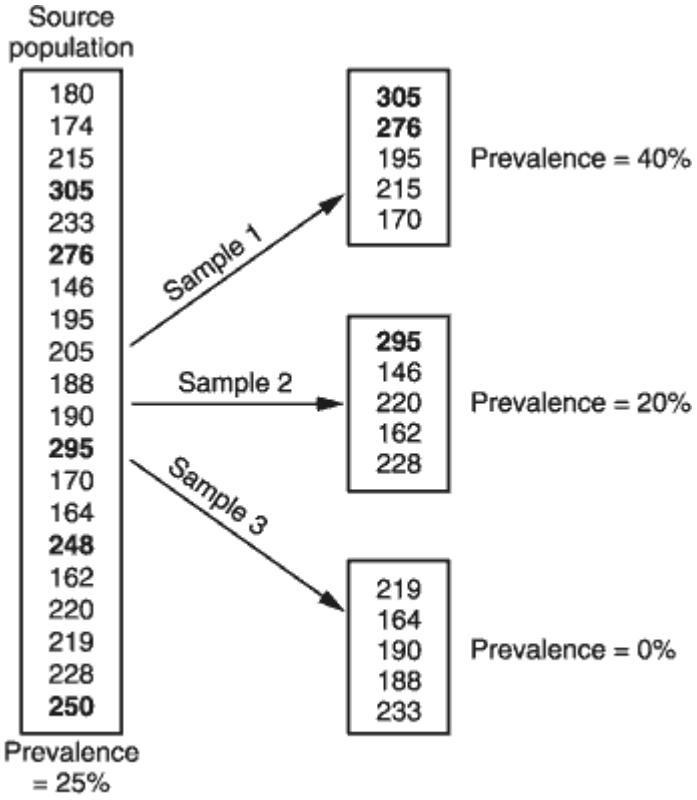
참 값 = 관측값 + “오차”

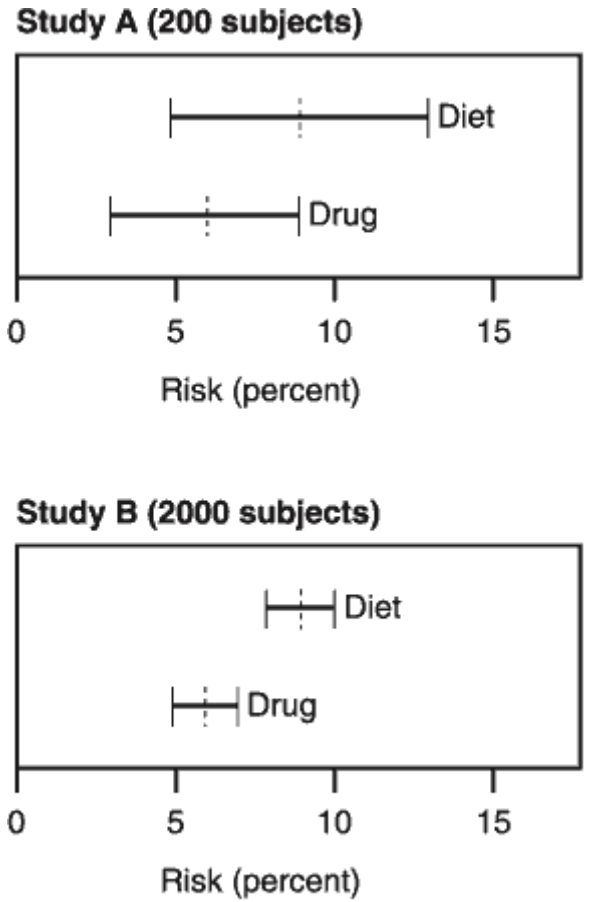


Random error

- **The defining characteristic of random error is that it is due to "chance" and, as such, is unpredictable**
  - **Ex) tossing a coin 100 times where the aim is to test the hypothesis that the coin is "fair"**
    - **to completely eliminate random error → toss the coin an "infinite" number of times**

- **Clinical or Epidemiologic studies: randomly sampled from a "population."**
  - **the null hypothesis is rejected when it is true: type I error (α)**
  - **the null hypothesis is not rejected when it is false: type II error (β)**
  - ***α and β = 0 ?***
    - **For a given sample size there is a tradeoff between type I error and type II error**





The effect of sample size on precision of risk estimates

Systematic error

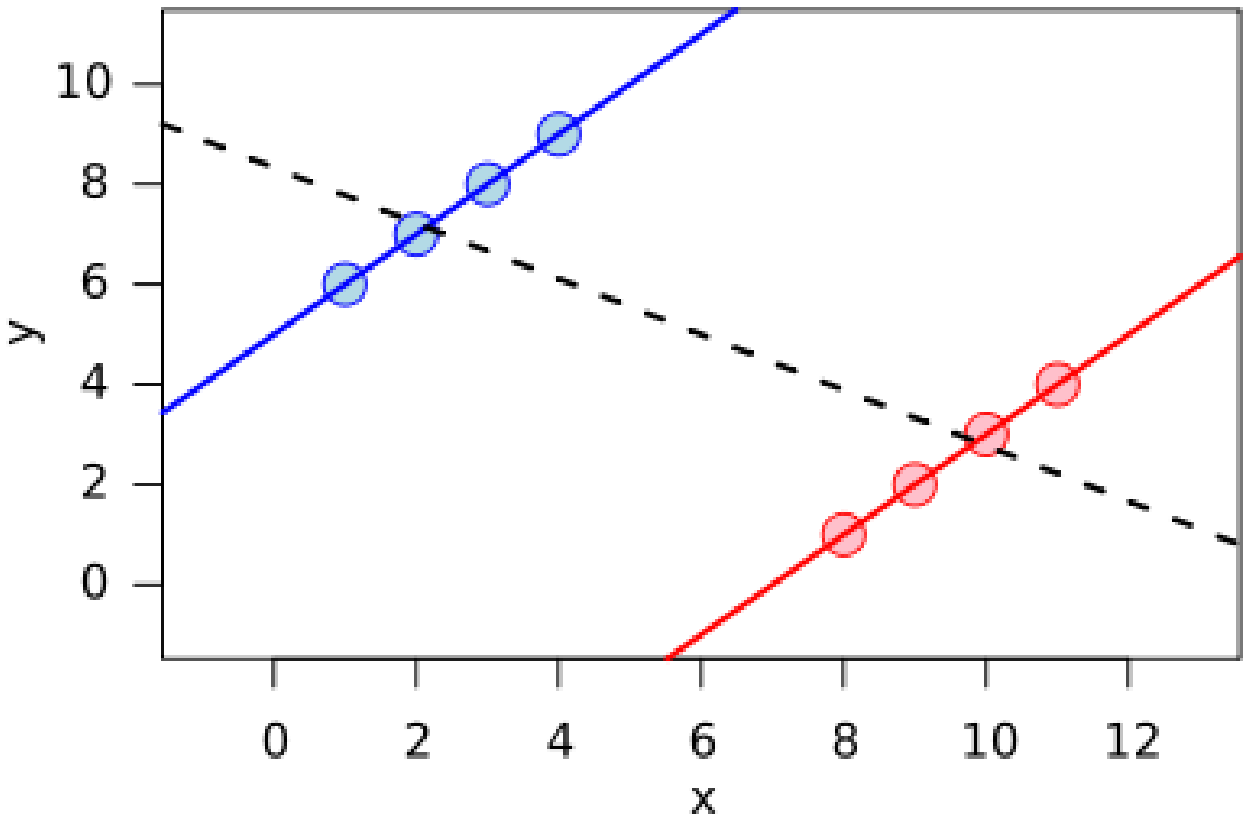
- **Systematic error: reproducible**
- **Result of problems having to do with study methodology**
  - **the study sample could be chosen improperly**
  - **the questionnaire could be invalid**
  - **the statistical analysis could be faulty**

- **Bias, Confounding**

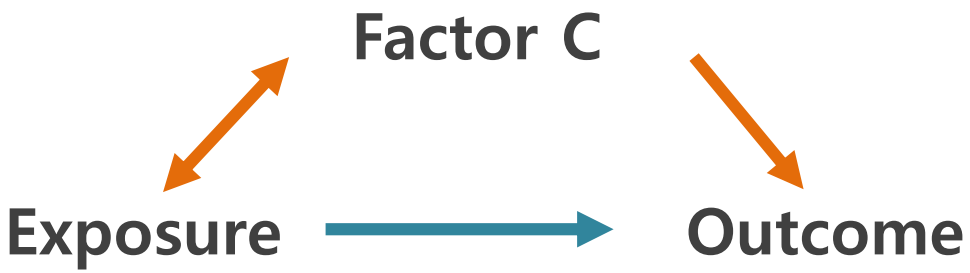
Counterfactual

The concept of causality has an important place in discussions of confounding (Pearl, 2000, Chapter 6). The idea of what it means for something to "cause" something else is a topic that has engaged philosophers for centuries. Holland (1986) and Greenland et al. (1999) review some of the issues related to causality in the context of inferential statistics. A helpful way of thinking about causality is based on the concept of counterfactuals. Consider the statement "smoking causes lung cancer," which could be given the literal interpretation that everyone who smokes develops this type of tumor. As is well known, there are many people who smoke but do not develop lung cancer and, conversely, there are people who develop lung cancer and yet have never smoked. So there is nothing inevitable about the association between smoking and lung cancer, in either direction. One way of expressing a belief that smoking is causally related to lung cancer is as follows: We imagine that corresponding to an individual who smokes there is an imaginary individual who is identical in all respects, except for being a nonsmoker. We then assert that the risk of lung cancer in the person who smokes is greater than the risk in the imaginary nonsmoker. This type of argument is termed counterfactual (counter to fact) because we are comparing an individual who is a known smoker with the "same" individual minus the history of smoking.

Simpson’s paradox



Confounding



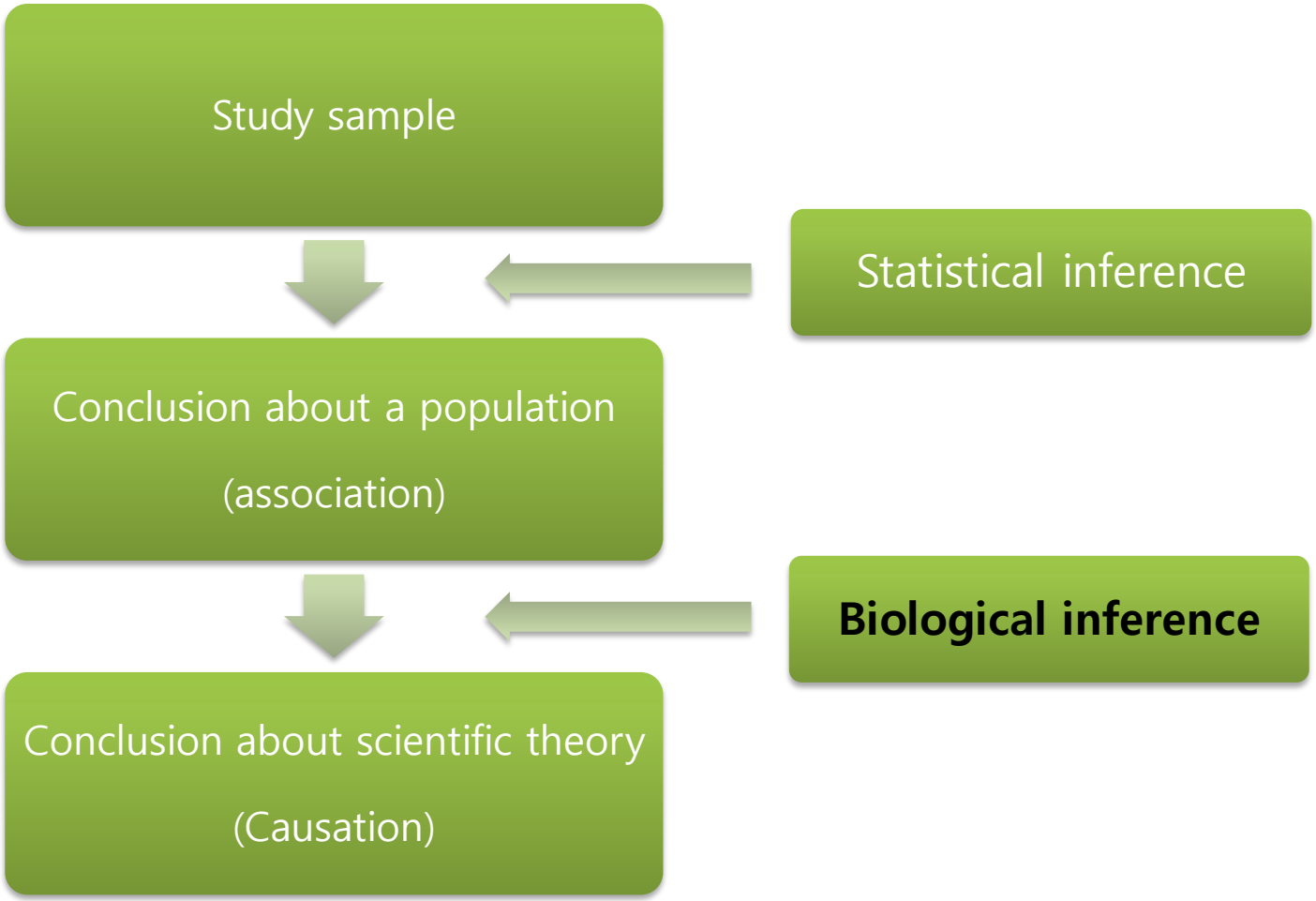
- Factor C must have an association with the outcome
  i.e. it should be a risk factor for the outcome;
- Factor C must be associated with the exposure,
- i.e. it must be unequally distributed between the exposed and non-exposed groups; and
- Factor C must not
  be a factor in the causal pathway of the outcome

CAUSATION?

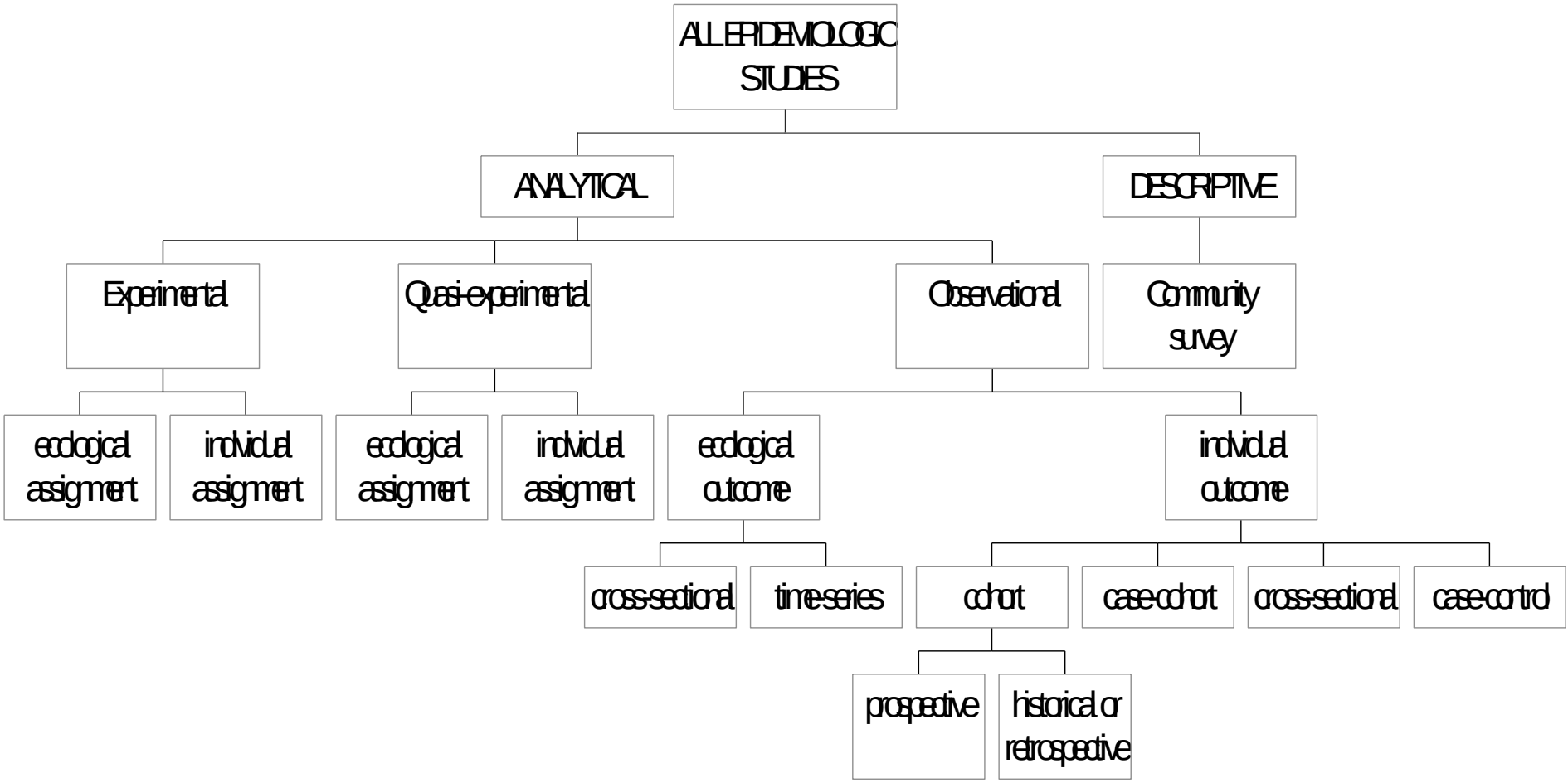
Causation

- **Risk factor:** exposure that increases the chance of an event such as death or disease happening
  - Risk factor is associated with the disease
- Risk factor might or might not be a cause of the disease

Overview of the scientific method



TYPOLOGY OF STUDY DESIGN



Study designs

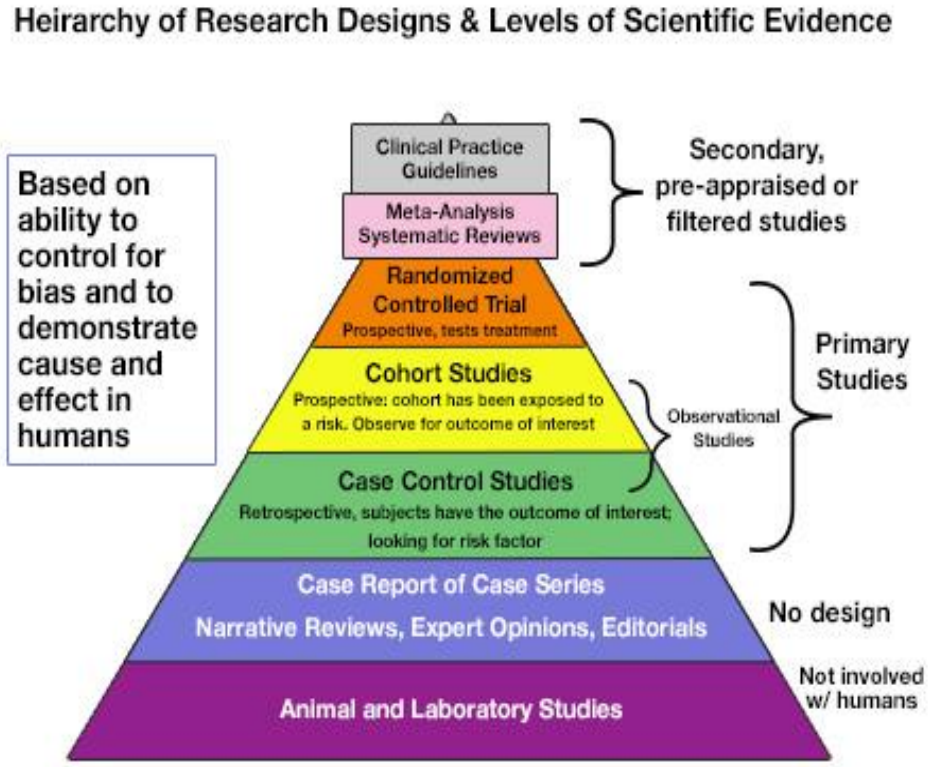
Observational study		Unit of study
Descriptive study	Hypothesis	
Analytical study	Hypothesis	
Ecological study, Correlation study		Population
Cross-sectional study, Prevalence study		Individuals
Case-control study, Case-reference study		Individuals
Cohort study, Follow-up study, Prospective study		Individuals
Experimental study, Intervention study		
Experiment		
Randomized controlled trials, Clinical study		Patients
Field trials		Healthy people
Community trials, Community intervention study		Community

Intervention

Study design

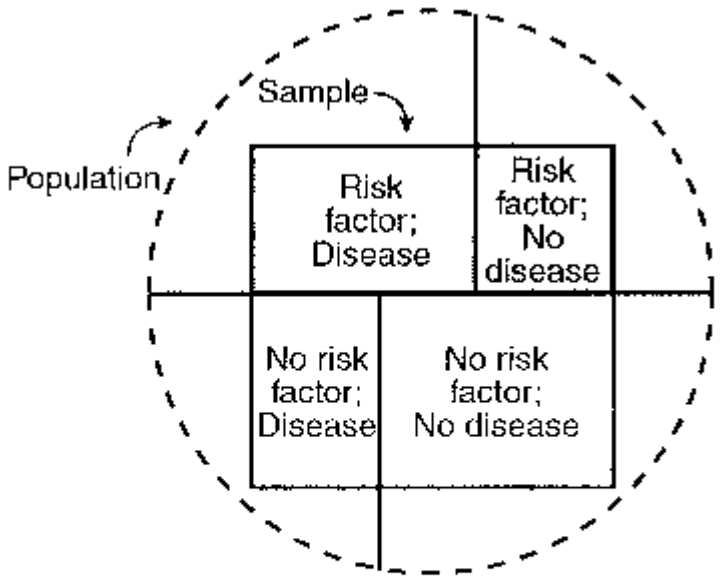
- Clinical trial
  - Is it possible?

- **Observational study**
  - the investigator does not determine the assignment of exposure, but instead passively observes events as they unfold.



Cross-sectional study

Cross-sectional study



- Total target groups or population
- Simple random sampling or systematic, stratified, or cluster sampling

■ **FIGURE 8.1**

In a cross-sectional study, the investigator: (a) selects a sample from the population, and (b) measures predictor and outcome variables (e.g., presence or absence of a risk factor and disease).

CS study may be concerned with:

- the presence of disorders, such as diseases, disabilities, and symptoms of ill health
- dimensions of positive health, such as physical fitness
- other attributes relevant to health, such as blood pressure and body measurements
- factors associated with health and disease, such as exposure to specific environmental factors, defined social and behavioural attributes (including health practices and attitudes to health and health services), and demographic characteristics; the correlates may be determinants, predictors, or effects of health and disease states.

Descriptive, analytical, or both

- **At a descriptive level, it yields information about a single variable about each of a number of separate variables in a total study population, or in specific population groups.**

- **At an analytical level, it provides information about the presence and strength of associations between variables, permitting the testing of hypotheses about such associations.**

Statistical measures

- **Descriptive statistic**
- **Prevalence: point, period, lifetime**
- **Association**
  - **Odds ratio**
  - **Rate ratio**
    - **prevalence ratio, exposure ratio**
  - **Rate difference**
    - **Prevalence difference**
    - **Exposure difference**
    - **Number needed to treat (NNT): number needed in unexposed group to avoid one case: 1/prevalence difference**

Common source of bias

- **Selection bias**
  - **Failure to choose a representative sample**
- **Information bias**
  - **Lack of clear diagnostic criteria**
  - **Operational definition**

Cross-sectional study: uses in community health care

- **Community diagnosis**
- **Health status**
- **Determinants of health and disease**
- **Association between variables**
- **Risk markers**
- **surveillance**

Case-control study

The sophisticated use and understanding of case-control studies is the most outstanding methodologic development of modern epidemiology. (Rothman 1986, p. 62)

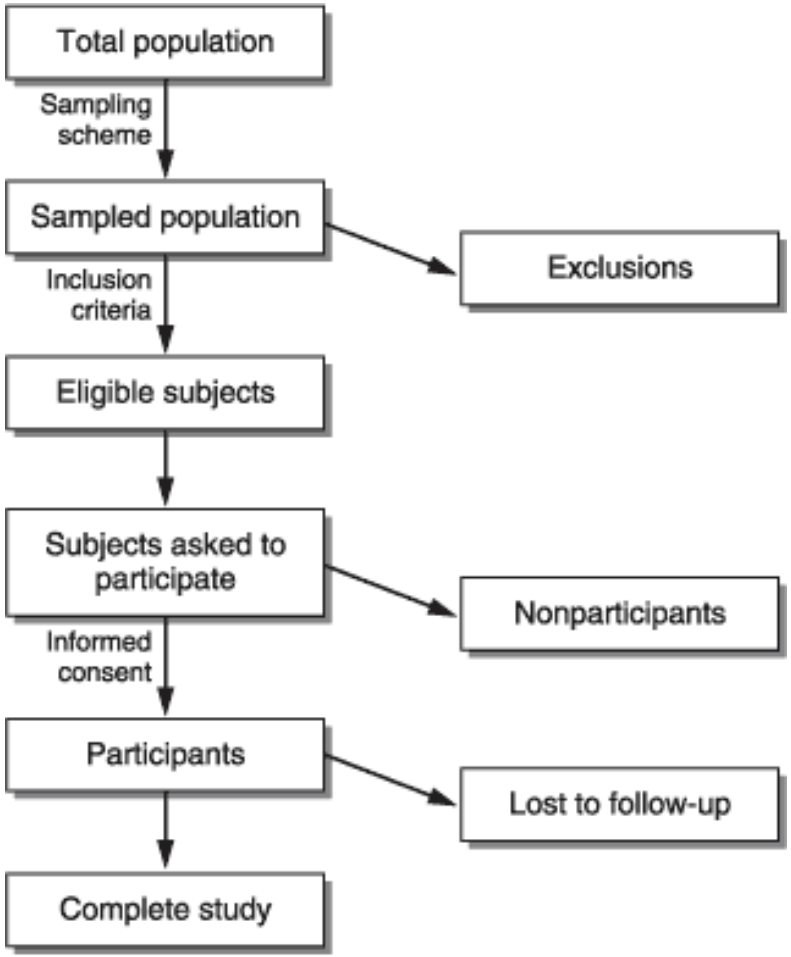
Select Study Design to Match the Research Goals

Objective	Design
Description of disease or spectrum	Case series or report Cross-sectional study
Determine operating characteristics of a new diagnostic test	Cross-sectional
Describe prognosis	Cohort study
Determine cause-effect	Cohort study **Case-control study**
Compare new interventions	Randomized clinical trial
Summarize literature	Meta-analysis

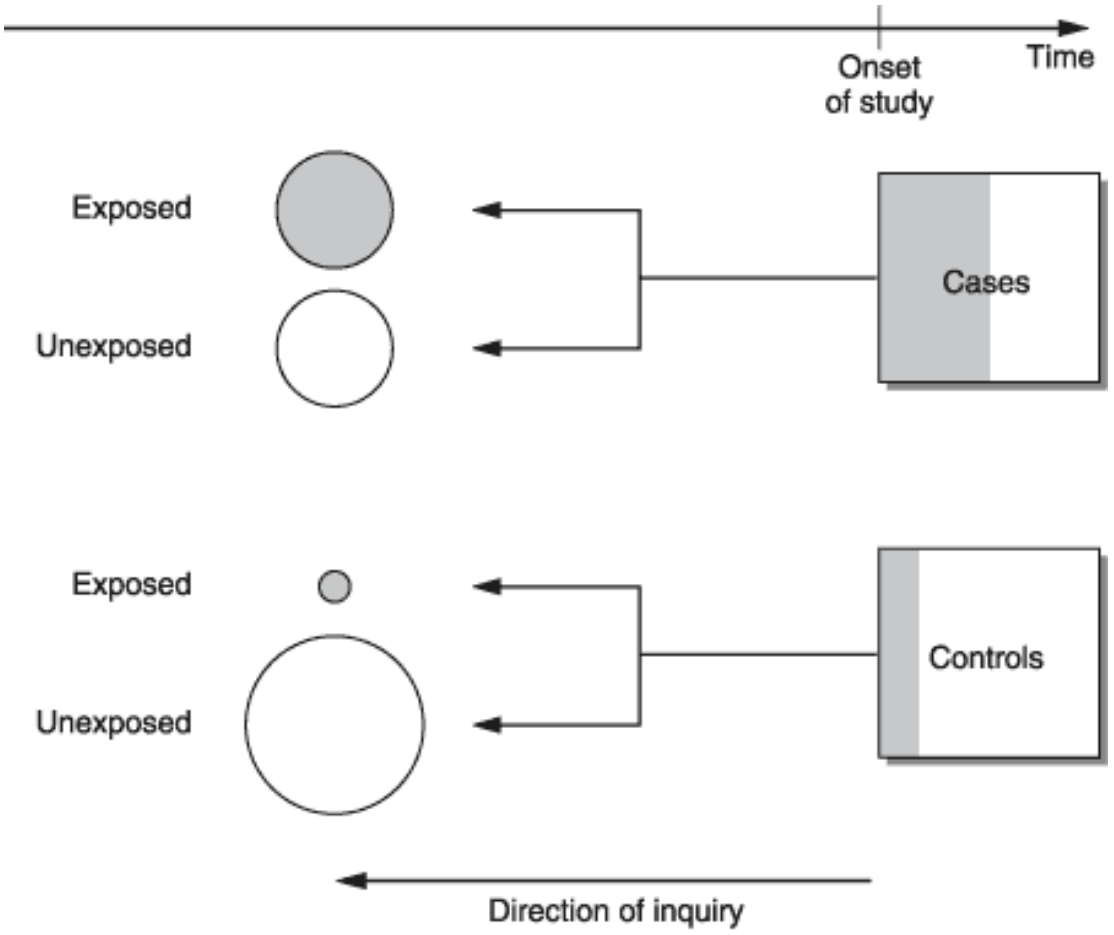
Basic design concept

- **First step**
  - **detect a number of people with the disease under study: the cases**
- **Second step**
  - **select a number of people who are free of the disease: the controls**


New cases of the disease
No medical attention
Seen elsewhere
Seen but misdiagnosed
Death or remission before diagnosis
Cases available for case-control study


Total population
Sampling scheme
Sampled population
Exclusions
Inclusion criteria
Eligible subjects
Subjects asked to participate
Nonparticipants
Informed consent
Participants
Lost to follow-up
Complete study

Case-Control Study Design



Variants of Case-Control Designs

- Case-control design
- Case-control studies within cohorts
  - Nested case-control study design
  - Case-cohort study design
- Case-parent study design
- Case-only study design

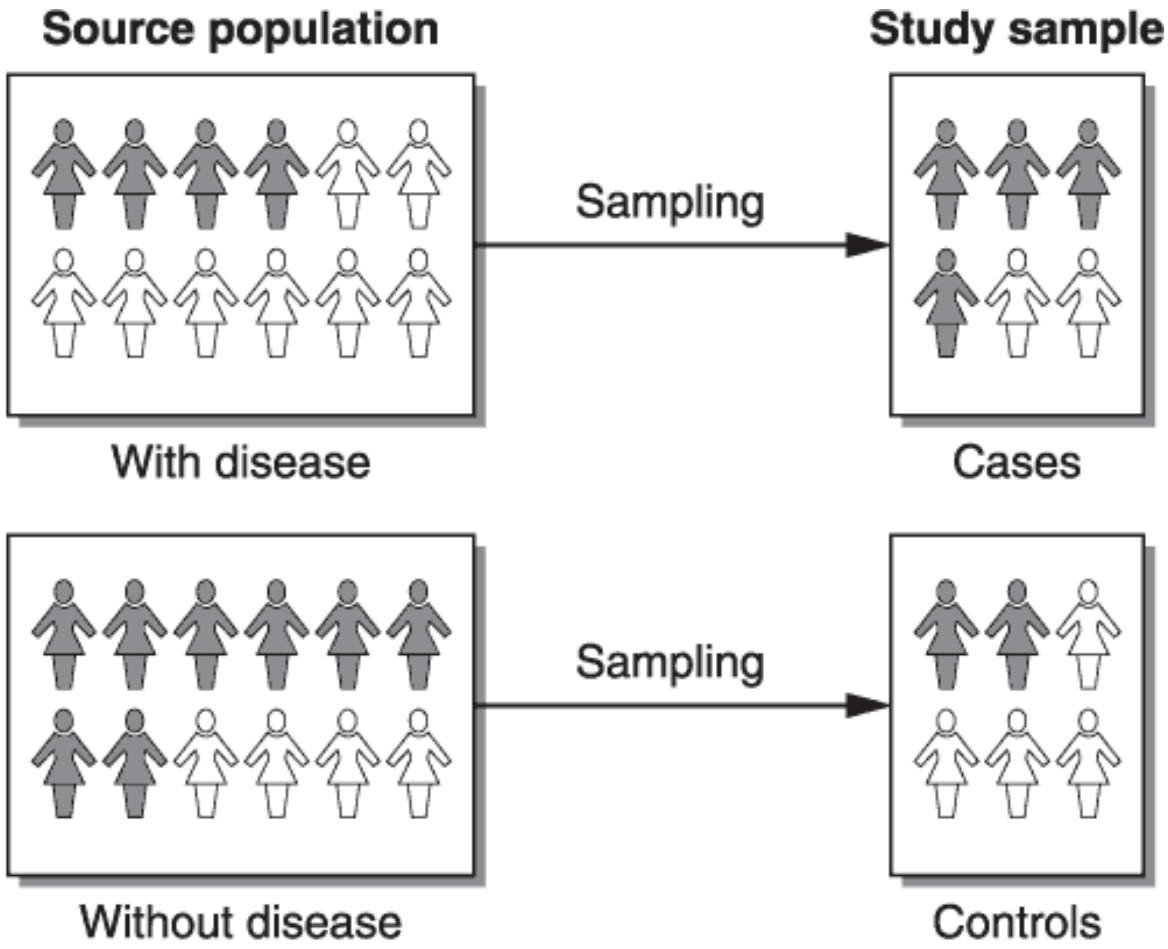
Case Control Study: Selection of Controls

- **Sources of controls**
  - Hospital controls
    - Hospitalized patients, best if chosen from the same hospital as cases in order to control for unknown reference population
    - all patients admitted to the hospital
    - specific diagnosis
  - Community control group
    - Probability sample best, but not often practical
    - Select from school rosters, insurance companies, etc.
    - Neighbors of cases
    - Random digit dialing
    - Best friend

Case Control Study: Selection of Controls

- **Multiple controls**
  - Controls of the same type
    - May improve precision of the measure of association
    - Precision rarely improved with more than 5 controls per case
  - Controls of Different Types
    - Hospital controls and community controls per case

- **Controls cannot be selected based on known or unknown association with exposure(s) or risk factors of interest**


Source population
Study sample
Sampling
With disease
Cases
Sampling
Without disease
Controls

Case-Control Study: Assessing Exposure

- Exposure is determined in a '**retrospective'** manner, that is one must look back in time to assess exposure status before a person became a case.

- **Exposure must be measured in a blinded manner**
  - Data collectors must be unaware of whether subject is a case or control
  - Data collectors should be unaware of the study hypothesis

Example: control selection

- **Coffee and pancreatic cancer, MacMahon B et al. NEJM 1981**
  - Coffee consumption was associated with pancreatic cancer
    - OR 2 – 3
    - Dose-response relationship
  - Controls were selected from other patients admitted to the hospital by the same physician as the case, often gastroenterologist
  - This specialist would admit patients with other diseases (gastritis or esophagitis) for which he or the patient would reduce coffee intake
  - Controls intake of coffee may be less than population - not representative of source population

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE ARCHIVE

Coffee and Cancer of the Pancreas

Brian MacMahon, M.D., Stella Yen, M.D., Dimitrios Trichopoulos, M.D., Kenneth Warren, M.D., and George Nardi, M.D.

N Engl J Med 1981; 304:630-633 | March 12, 1981 | DOI: 10.1056/NEJM198103123041102

Abstract

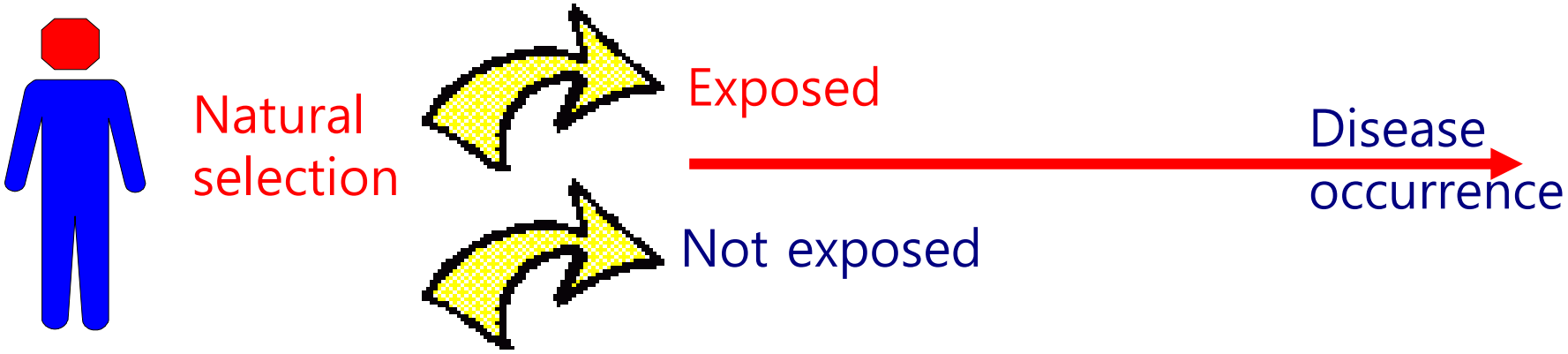
We questioned 369 patients with histologically proved cancer of the pancreas and 644 control patients about their use of tobacco, alcohol, tea, and coffee. There was a weak positive association between pancreatic cancer and cigarette smoking, but we found no association with use of cigars, pipe tobacco, alcoholic beverages, or tea. A strong association between coffee consumption and pancreatic cancer was evident in both sexes. The association was not affected by controlling for cigarette use. For the sexes combined, there was a significant dose-response relation ($P \sim 0.001$); after adjustment for cigarette smoking, the relative risk associated with drinking up to two cups of coffee per day was 1.8 (95 per cent confidence limits, 1.0 to 3.0), and that with three or more cups per day was 2.7 (1.6 to 4.7). This association should be evaluated with other data; if it reflects a causal relation between coffee drinking and pancreatic cancer, coffee use might account for a substantial proportion of the cases of this disease in the United States. (N Engl J Med. 1981; 304:630–3.)

Supported by a grant (5 P01 CA 06373) from the National Cancer Institute.

We are indebted to the administrative, nursing, and record-room staffs of Beth Israel Hospital, Carney Hospital, Lahey Clinic, Massachusetts General Hospital, New England Baptist Hospital, New England Deaconess Hospital, Peter Bent Brigham Hospital, Rhode Island Hospital, Tufts–New England Medical Center, University Hospital, and the Veterans Administration Hospital of Jamaica Plain, Mass.; to the physicians on their staffs who gave us permission to interview patients; and to Mrs. Kim Neave and Miss Mary Curran for conducting the

Cohort study

Cohort study

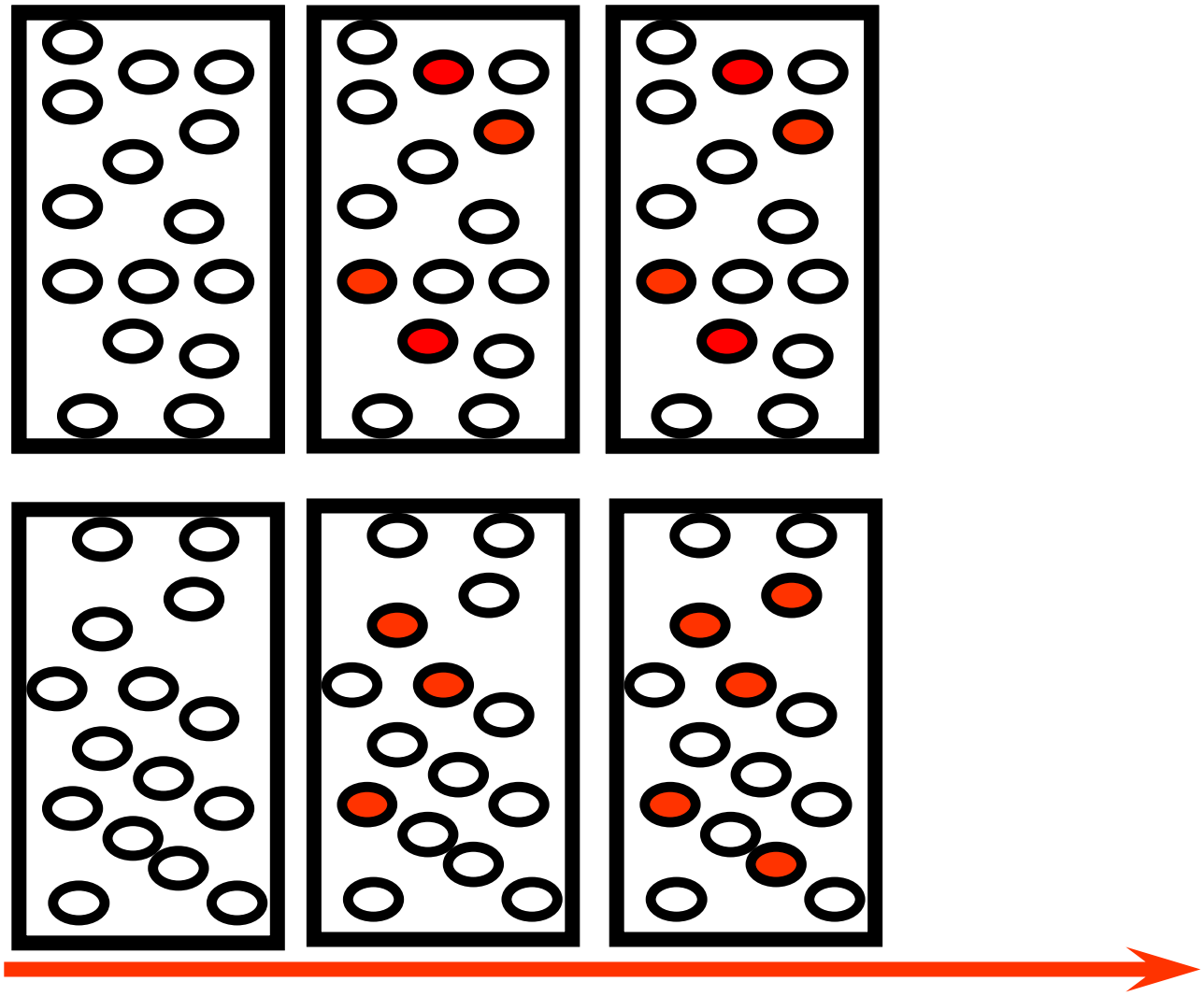


Unethical to perform experiments on people
if exposure is harmful

Cohort studies

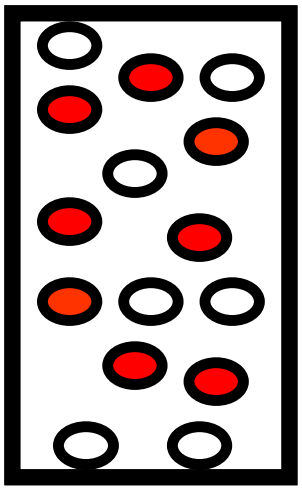
exposed

unexposed



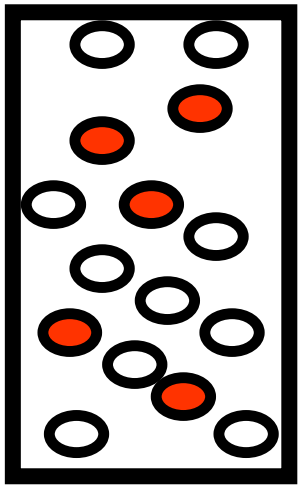
Cohort studies

exposed



Incidence among exposed

unexposed



Incidence among unexposed

Recipe: Cohort study

- **Identify group of**
  - **exposed subjects**
  - **unexposed subjects**
- **Follow up for disease occurrence**
- **Measure incidence of disease**
- **Compare incidence between exposed and unexposed group**

Cohort study: outcome measures

- **Incidence in the exposed**
- **Incidence in the unexposed**
- **Relative risk**
- **Attributable risk (risk difference)**
- **Population attributable risk**
- **Attributable risk percent**
- **Population attributable risk percent**
- **Standardized mortality ratio**

Cohort study: outcome measures

- Relative Risk: **$RR=I_e/I_o$**
  (strength, perhaps cause)
- Attributable Risk: **$AR=I_e-I_o$**
  (impact)
- Attributable Risk %: Attributable Fraction :**AR%=(Ie-Io)/Ie = (RR-1)/RR**

IMPORTANT CONCEPTS

- **Rates Versus Risks**

- **Calculating Person Time**

Rates Versus Risks

Among persons with acute leukemia, does antibiotic treatment prevent or delay the onset of gram-negative bacterial infections (as measured by the presence of fever).

--- 35 patients receive antibiotic treatment

all 35 develop fever

260 person days of follow-up

--- 40 patients do not receive antibiotic

treatment all 40 develop fever

210 person days of follow-up

Rates Versus Risks

$Treatment_{YES}$

CI = 35 / 35 = 1.0 (100%)

IR = 35 / 260 = 0.1346 / person day

$Treatment_{NO}$

CI = 40 / 40 = 1.0 (100%)

IR = 40 / 210 = 0.1905 / person day

Risk Ratio = 1.0 / 1.0 = 1.0

Rate Ratio = 0.1346 / 0.1905 = 0.7066

summary

Some examples of errors in design

- **Definite errors**
  - **Failure to use randomization in a controlled trial**
  - **Use of an inappropriate control group**
  - **Failure to anticipate regression to the mean**

- **Matters of judgement**
  - **Is the sample size large enough?**
  - **Is the response rate adequate?**

- **Poor reporting**
  - **Study aims not stated**
  - **Justification of sample size not given**
  - **In a controlled trial, method of randomization not stated**

Altman DG. Statistical reviewing for medical journals. Statistics in medicine 1998;17:2661-2674

연구주제에 따른 연구설계 선택 (not absolute)

- 새로운 가설을 만들 때
  - 가능한 모든 방법 활용
  - 기술연구와 분석연구 모두 가능
  - Case report, Case-series report
- 가설을 가지고 하는 연구
  - 가설을 명확히 할 것
  - 원인(위험요인, Exposure)이 무엇인가?
  - 결과(질병, Outcome)이 무엇인가?
  - 임상시험(?) > 코호트 > 환자·대조군 > 단면

연구주제에 따른 연구설계 선택 (not absolute)

- 원인(위험요인)의 특성에 따라
  - 변하지 않는 원인 (유전, 성별, 인종…): 단면연구 OK
  - 회상편견적은 원인 (가족력, 흡연…): 환자·대조군 OK
  - 과거 객관적 기록 [직업적 노출…): 후향적 코호트

- 결과(질병)의 특성에 따라
  - 드문 질병: 환자·대조군 연구
  - 유병률 높은 질병: 단면 연구
  - 발생률 높은 질병: 코호트 연구
  - 확진된 환자만 있는 경우(암센터): 환자·대조군

연구주제에 따른 연구설계 선택 (not absolute)

- 이차예방/치료 효과 평가
  - 임상시험 > 코호트 > 환자·대조군
  - 윤리적 문제가 없는가?
  - Randomization이 가능한가?
  - 관찰기간은 얼마나 필요한가?
  - 기존 발표된 논문들의 연구 설계는?
- 예후, 예후인자 파악
  - 전향적 코호트, 후향적 코호트

감사합니다.